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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 20041213

Application Number: 09/664,326
Filing Date: September 18, 2000
Appellant(s): HABERMANN ET AL.

Anthony C. Tridico, Reg. No. 45,958
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed October 24, 2003.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The appellant's statement that the rejection of claims 6, 7, and 9 stand or fall together is correct.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Achstetter et al. "A new signal peptide useful for secretion of heterologous proteins from yeast and its application for synthesis of hirudin" Gene, Vol. 110, pp. 25-31.

EP 0 448 093	SCHMID et al.	03-21-1991
5,919,895	SCHMID et al.	07-06-1999 (English Language equivalent of EP 0 448 093)

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 6, 7, and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Achstetter et al. (Gene (1992) 110: 25-31) in view of Schmid et al. EP 0 448 093 (1990; cited in IDS of Paper No. 4).

The examiner notes that U.S. Patent No. 5,919,895 ('895 patent) has been used as the English language equivalent of EP 0 448 093. Therefore, references to Schmid et al. will refer to the '895 patent.

Achstetter et al. disclose a method of selecting a signal peptide for secretory expression of hirudin or a hirudin derivative (p. 26, Col. 1, lines 27-30) comprising (a) expressing in a culture medium, hirudin having antithrombotic activity, and which has a defined amino acid, aa_x, at its N terminus, wherein said amino acid aa_x, is connected via its N-terminal to a signal peptide to be tested; (b) determining the expression rate by measuring protein activity in the culture supernatant; (c) repeating steps (a) and (b) with various signal peptides; and (d) selecting the suitable signal peptide by comparing the expression rates represented by the hirudin antithrombotic activity found in step (b). It is noted that Claim 6 does not provide any reference sequence to determine whether the "defined amino acid, aa_x" is an extra amino acid in addition to the 65 or 66 amino acids of the native hirudin sequence or if it is just the N-terminal amino acid of hirudin. Native hirudin contains either 65 or 66 amino acids and a hirudin derivative could contain any number of amino acids. Therefore, the limitation "which has a defined amino acid, aa_x, at its N-terminus, wherein said amino acid, aa_x is connected via its N-terminal to a signal peptide" is considered to encompass any signal peptide-hirudin protein wherein the signal peptide is at the N-terminus. Thus, the hirudin protein described in the method of Achstetter et al. is considered to have a defined amino acid, aa_x, at its N-terminus, wherein said amino acid aa_x is connected via its N-terminal to a signal peptide to be tested.

Achstetter et al. teach that the selection method involves expression in yeast and do not teach that the method involves expression in *E. coli*.

Schmid et al. teach that the expression of hirudin in *E. coli* would be advantageous over processes known in the art using yeast because "the cultivation of yeast cells takes longer and is more demanding than that of bacteria, for example, *E. coli* (Col. 2, lines 15-16). The bacteria, *E. coli*, appears to be preferred because of the availability of *E. coli* strains which show massive protein secretion into the culture medium (Col. 3, lines 32-34). Schmid et al. disclose a method of expressing Ala-hirudin derivatives in *E. coli* (Col. 6, lines 1-11) and suggest hirudin derivatives having any one of the amino acids Leu, Ile, Ala, Val, Gly, Ser, Asp, Glu, Asn, Gln, His, Met, Phe, and Tyr at the N-terminus wherein the amino acid is connected via its N-terminal to a signal peptide (Col. 2, lines 51-67). Schmid et al. state it is possible to obtain 2 g/L of a hirudin derivative with the N-terminal sequence of SEQ ID NO :1 (Ala-hirudin) in the culture supernatant of an *E. coli* secretor (Col. 3, lines 32-35).

Therefore, it would be obvious to one of ordinary skill in the art at the time of the invention, to practice the method of selecting signal peptides for the secretory expression of hirudin described in Achstetter et al. in *E. coli* using a aa_x-hirudin sequence as disclosed in Schmid et al. One of ordinary skill in the art would have been motivated to use *E. coli* in the method of selecting signal peptides because Schmid et al. state that the cultivation of yeast cells takes much longer and is more demanding than bacteria. Moreover, Schmid et al. shows that the method disclosed therein is highly successful in producing high concentrations of active Ala-hirudin (see Col. 3, lines 24-26). Thus, it appears that the claims are unpatentable over Achstetter et al. in view of Schmid et al. for the reasons cited above.

(11) Response to Argument

For the above reasons, it is believed that the rejections should be sustained.

References should be considered for what they teach as a whole.

Appellants argue that neither of Achstetter et al. or Schmid et al. contains any motivation to combine the reference teachings and that the references teach away from such a combination. This argument has been considered but is not deemed persuasive because Appellants have not considered what the references teach as a whole. Appellants contend that Achstetter et al. is trying to achieve increased hirudin production while Schmid et al. teaches that yield is low in *E. coli*. However, as Appellant agrees (p. 6, last paragraph), when considered as a whole, Schmid et al. teaches that the use of *E. coli* in hirudin expression dramatically improves yield and simplifies the isolation process. When considered as a whole, the references show that those of ordinary skill in the art at the time of the invention 1) were well aware of screening assays to find optimal signal sequences in hirudin expression (see Achstetter et al.); 2) were interested in improving hirudin expression (Schmid et al. and Achstetter et al.); 3) recognized that *E. coli* expression systems offered quicker and less demanding processing than yeast (see Schmid et al.); 4) with the disclosure of Schmid et al., knew of a construct that encoded a hirudin derivative fused to a signal peptide that could be expressed in an *E. coli* expression system and obtained at up to above 2g/L; and 5) as suggested by Schmid et al., that additional constructs having various N-terminal amino acids and various signal peptides would also result in high level

expression and secretion of hirudin. Thus, one of ordinary skill in the art at the time of the invention would have been motivated to use a screening assay as described in Achstetter et al. to find a signal peptide that would provide optimal expression and secretion of the hirudin derivatives disclosed in Schmid et al.

Limitations from the Specification are not read into the claims.

Present claims do not exclude expression in E. coli secretion mutants and such secretion mutants are used in Examples of the present Specification.

Appellants argue that Schmid et al. overcomes the problems of low expression in *E. coli* by using an *E. coli* secretor mutant.

First, it is noted that the features upon which Appellant relies (i.e., exclusion of *E. coli* secretor mutants) are not recited in the rejected claim(s). The claims do not exclude the use of *E. coli* secretor mutants but encompass expression in any *E. coli* culture medium. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). In fact, in the present case, the Specification does not even contain a limitation that excludes the use of secretion mutants in the method of the invention because all of the examples in the present Specification use the *E. coli* secretor mutant WCM 100 (see Specification, Ex. 1, p. 9, lines 1 and 5; Ex. 2, p 9, line 24; Ex. 3, p. 10, line 20; Ex. 4, p. 11, line 20; Ex. 5, p. 12, line 18; Ex. 6, p. 13, line 22; Ex. 7, p. 14, line 22; Ex. 8, p. 15, line 19; Ex. 9, p. 16, line 18; Ex. 10, p. 17, line 12).

Second, contrary to Appellants assertions, Schmid et al. does not state that the *E. coli* secretor mutants were essential to the increased expression obtained. In fact, Schmid et al. implies that the sequences of the hirudin derivatives were more important for the high yields obtained. (For, example see paragraph bridging Col. 3-4 discussing the various signal sequences that allow secretion; and Summary of the Invention which implies that it is the combination of the *E. coli* secretor mutants and the specific hirudin derivatives disclosed that allows for increased expression and secretion; and Col. 3, lines 24-26).

The Claims encompass the testing of any signal peptide.

Appellants argue that there is no motivation to use the yeast signal peptides of Achstetter et al. in the Schmid et al. system which is optimized for *E. coli* signal peptides. As stated in the Office Action mailed January 7, 2003 (p. 11, last paragraph), the claims are not limited to the type of signal peptides that are used in the method. In fact, the claimed methods are used to find signal peptides and thus are open to the testing of any signal peptide sequence. Appellants have responded that both references as a whole teach that in order to obtain a higher yield of hirudin, one must use either yeast signal peptides (Achstetter et al.) or *E. coli* secretor mutants (Schmid et al.) and that the Examiner cannot advocate the removal of both or assert the exclusion of one (see p. 8 of Appeal Brief filed October 4, 2003). First, this argument assumes that one of ordinary skill in the art would have understood from Schmid et al. that the secretor mutants alone were responsible for the increased expression. This is not the

case as the *E. coli* secretor mutants were already known in the art prior to Schmid et al. (see references in Schmid et al. at Col. 3, lines 32-36) yet Schmid et al. still indicate a need in the art for increased expression of hirudin in *E. coli* and concludes that the disclosed hirudin derivatives can be obtained from *E. coli* expression at high yield. Second, Schmid et al. discloses several signal peptides that may be used with the disclosed hirudin derivatives (paragraph bridging Col. 3-4). Thus, one of ordinary skill in the art was aware of various signal peptides and their function in protein secretion; and one of ordinary skill in the art would have been motivated to optimize the expression of hirudin by testing the other signal peptides disclosed in Schmid et al. using the screening assay described in Achstetter et al.

There would have been an expectation of success in practicing a method of screening for signal peptides as taught in Achstetter et al. using the hirudin derivatives and E. coli expression system of Schmid et al.

Appellants argue that one of ordinary skill in the art would have expected that removing the *E. coli* secretor mutant strains from the invention of Schmid et al., one would simply be left with the same low-yield *E. coli* known in the art. Thus, there is no reasonable expectation in either Achstetter et al. or Schmid et al. that practicing Achstetter's process in the prior art non-mutated *E. coli* of Schmid et al. would result in successful practice of the claimed invention. This argument has been considered but is not deemed persuasive because, first, removal of *E. coli* secretor mutant strains from the invention of Schmid et al. is not required for Schmid et al. to meet the limitations of the present claims. The present claims encompass expression in any *E. coli* culture

medium and do not exclude *E. coli* secretor mutants. In fact, all of the examples in the present Specification all of the examples in the present Specification use the *E. coli* secretor mutant WCM 100 (see Specification, Ex. 1, p. 9, lines 1 and 5; Ex. 2, p 9, line 24; Ex. 3, p. 10, line 20; Ex. 4, p. 11, line 20; Ex. 5, p. 12, line 18; Ex. 6, p. 13, line 22; Ex. 7, p. 14, line 22; Ex. 8, p. 15, line 19; Ex. 9, p. 16, line 18; Ex. 10, p. 17, line 12). Second, as stated above, Schmid et al. does not indicate that the *E. coli* secretor mutants were the cause of obtaining higher yield. The *E. coli* secretor mutants were already known in the art prior to Schmid et al. (see references in Schmid et al. at Col. 3, lines 32-36); yet Schmid et al. still indicates a need in the art for increased expression of hirudin in *E. coli* and concludes that the disclosed hirudin derivatives can be obtained from *E. coli* expression at high yield. Thus, Schmid et al. does not suggest that removal of the *E. coli* secretor mutants disclosed therein would have led to the previous low levels of hirudin expression.

Therefore, one of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success in practicing a screening assay for signal peptides as described in Achstetter et al. using the *E. coli* system and hirudin constructs taught in Schmid et al. since Schmid et al. shows that doing so results in high levels of hirudin expression and suggests various other signal peptides that can be used to achieve such high level expression.

In Conclusion

Both Achstetter et al. and Schmid et al. teach the desire in the art for improved expression of hirudin. Schmid et al. teach that *E. coli* systems would be advantageous over yeast because *E. coli* cultivation does not take as long and is less demanding (Col. 2, lines 15-16) but that the prior art had problems getting high protein yields using *E. coli*. Schmid et al. improve this prior art problem of low yields with the discovery of a new hirudin derivative that can be expressed at high yields in *E. coli* (Col. 3, lines 24-26). Schmid et al. suggest that other constructs encoding hirudin with various N-terminal amino acids and fused to various signal peptides would give similar yields of hirudin. One of ordinary skill in the art would have been motivated to use the signal peptide-screening assay disclosed in Achstetter et al. to further optimize the expression of hirudin disclosed in Schmid et al. Optimization of a previously known expression system is not considered patentable. Thus, the rejection has been maintained.

Respectfully submitted,

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January 20, 2004

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